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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/821,240	04/08/2004	Nisar Ahmed Khan	2183.03-6384US	9732

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EXAMINER	
SKOWRONEK, KARLHEINZ R	
ART UNIT	PAPER NUMBER
1631	

NOTIFICATION DATE	DELIVERY MODE
10/09/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USPTOMail@traskbritt.com

Office Action Summary	Application No.	Applicant(s)	
	10/821,240	KHAN ET AL.	
	Examiner	Art Unit	
	KARLHEINZ R. SKOWRONEK	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 June 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27,48,50 and 51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27,48,50 and 51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Status

Claims 27, 48, 50, and 51 are pending.

Claims 1-26, 28-47, 49, and 52 are cancelled.

Claims 27, 48, 50, and 51 have been examined.

Claims 27, 48, 50, and 51 are rejected.

Claim Rejections - 35 USC § 103

Response to Arguments

Applicant's arguments, see remarks, p. 5-7, filed 30 June 2008, with respect to the rejection(s) of claim(s) 27 and 47-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ivanov et al. (IDS filed 4/12/2006, ref No. 1), in view of Werner et al. (Experientia Vol. 42, p. 521-531, 1986), in view of Lam et al. (US PAT 5,650,489), in view of Houghten et al. (DDT, Vol. 5, No. 7, p. 276-285, July 2000) and in view of Lin et al. have been fully considered and are persuasive . Therefore, the rejection has been withdrawn in view of the amendments to the claims cancelling the Markush group members of glucose tolerance and the release of other inflammatory mediators.

However, upon further consideration, a new ground(s) of rejection is made in view of Cillari et al. which shows that a property of the tetrapeptide, tuftsin, is the modulation of nitric oxide production.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The following rejection is necessitated by amendment of the claims.

Claims 27, 48, and 50-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ivanov et al. (IDS filed 4/12/2006, ref No. 1), in view of Werner et al. (Experientia, Vol. 42, p. 521-531, 1986) and Cillari et al. (Infection and Immunity, Vol.

62, No. 6, p 2649-2652, June 1994), in view of Lam et al. (US PAT 5,650,489), in view of Houghten et al. (DDT, Vol. 5, No. 7, p. 276-285, July 2000) and in view of Lin et al.

The claims are directed to a method of producing a pharmaceutical comprising identification of a protein that is cleaved into fragments consisting of 3 or 4 amino acids that have an activity; analyzing the fragment for biological activity; entering data from biological activity analysis of the peptide into a database; determining the identity of a peptide that modulates septic shock, release of inflammation mediators, NF-kappa B regulation, regulation of sepsis, nitrate production, nitric oxide production, glucose tolerance, or combinations, conducting therapeutic profiling for efficacy and toxicity; and formulating a pharmaceutical preparation. In an embodiment, the peptide activity is different from the active of the protein from which it is derived.

Ivanov et al. shows the identification of hemoglobin as a source of biologically active peptides (p. 172, col. 2). Ivanov et al. shows that peptides derived from hemoglobin are 3-9 amino acids in length (figure 4). Ivanov et al. shows that the biological activity analysis is entered in to a database which is shown in the forma of tables (table VII and VIII). Ivanov et al. suggest that the endogenous fragmentation of hemoglobin and consequent formation of biologically active peptides is not an isolated phenomenon; rather it is shared among other proteins such as cytochrome C oxidase, immunoglobulins, albumin, fibrinogen, and others (p. 186, col. 1).

Werner et al. shows immuno-modulating peptides can be derived from the proteolytic degradation of proteins. Werner et al. shows that the tetrapeptide tuftsin is derived from the Fc region of Leukokinin through its proteolytic degradation with tuftsin-

endopeptidase and leukokininase (p. 525-526, col. 2). In an embodiment, Werner et al. shows that the activity of Tuftsin is different from the activity of antibody from which it is derived (p. 526, col. 2). Werner et al. shows fibronectin is degraded by plasminogen to formfibrinogen degradation products having immuno-modulatory activity (p. 526-527, col. 1). Werner et al. shows that proteolytic digestion of human casein produced peptide fragments that have immuno-modulatory activity (p. 528, col. 1). Werner et al. also shows that tripeptides were also identified with immuno-modulatory activity (p. 528, col. 1). Werner et al. shows that the tripeptide TKP which is a proteolytic cleavage product of tuftsin, modulates the release of the inflammation mediator IL-1 (p. 526, col. 2). Werner et al. suggest that immuno-modulatory peptides may be useful as drugs (p. 529, col. 2).

Cillari et al. shows that Tuftsin modulates nitric oxide production (figure 1). Cillari et al. successfully shows that tuftsin modulates nitric oxide production. Cillari et al. shows it is beneficial to identify agents that increase nitric oxide production because nitric oxide has antimicrobial activity (p. 2649, col. 1).

Ivanov et al. and Werner et al. do not show conducting therapeutic profiling for toxicity and efficacy or the formulation of a pharmaceutical preparation.

In Lin et al, compounds are identified that modulate the signaling pathways that include ephrin-PDZ interactions (p. 2, [0020]) that provide a therapeutic benefit to diseases of the immune system such as sepsis and septic shock(p. 3, [0033]). One disclosed assay system is a search of members of a random peptide library reading on searching a peptide database (p. 15, [0158]). The identified compounds are profiled

therapeutically for efficacy toxicity and in animals (p. 2, [0021]). Suitable compounds are then formulated into a pharmaceutical preparation (p. 2, [0022]). Lin shows that peptides have therapeutic benefits and increased stability and reduced host immune recognition ([0094]).

Lam et al. shows a method of producing libraries of biopolymers of defined size and composition. Lam et al. shows that the method provides a powerful and faster way to identify useful biopolymers from a library (abstract). Lam et al. defines peptide to refer to a compound of 2 or more amino acids linked by peptide bonds (col. 7, line 58-62). Lam et al. shows that the synthesis of the library is performed in iterative manner allowing production of n-mers, peptides of any number of amino acids in length (col. 10, line 33-31). Lam shows the synthesis of a tetrapeptide library (col. 33, line 50-65). Lam et al. shows the peptide libraries can identify peptides that have immuno-modulatory activity (col. 31, line 35 to 32, line 67).

Houghten et al. shows searching tripeptide and tetrapeptide libraries (p. 279, col. 2). Houghten et al. shows searching using mixed compounds is beneficial in terms of time and cost savings as well as providing a way to rapidly screen compounds to identify highly active individual compounds (p. 279, col. 2).

It would have been obvious to one of skill in the art to modify the identification of proteins that are degraded to for biologically active fragments of 3-9 amino acids in length and specifically 3-4 amino acids in length of Werner et al. or Ivanov et al. with the method of producing pharmaceutical of Lin et al. because Lin et al. shows peptides have therapeutic benefits and increased stability and reduced host immune recognition.

It would have been further obvious to one of skill in the art to modify the identification of proteins that are degraded to biologically active fragments of 3-9 amino acids in length and specifically 3-4 amino acids in length of Werner et al. and Ivanov et al. with the method of producing pharmaceutical of Lin et al. because Werner et al. shows immuno-modulatory peptides may be useful as drugs and Ivanov et al. shows the endogenous fragmentation of hemoglobin and consequent formation of biologically active peptides is not an isolated phenomenon; rather it is shared among other proteins such as cytochrome C oxidase, immunoglobulins, albumin, fibrinogen, and others. It would have been further obvious to one of ordinary skill in the art to modify the identification of proteins that are degraded to biologically active fragments of 3-9 amino acids in length and specifically 3-4 amino acids in length of Werner et al. and Ivanov et al. with the modulation nitric oxide production of Cillari et al. because Cillari et al. shows it is beneficial to identify agents that increase nitric oxide production because nitric oxide has antimicrobial activity. It would have been further obvious to one of skill in the art to modify the method of producing a pharmaceutical that is based on peptide fragments of a protein's proteolytic degradation with the library of Lam et al. because Lam et al. shows it is a powerful and faster way to identify useful biopolymers from a library. It would have been further obvious to one of skill in the art to modify the method of producing a pharmaceutical that is based on peptide fragments of a protein's proteolytic degradation with tripeptide and tetrapeptide libraries of Houghten et al. because Houghten et al. shows searching using mixed compounds is beneficial in terms of time

and cost savings as well as providing a way to rapidly screen compounds to identify highly active individual compounds.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KARLHEINZ R. SKOWRONEK whose telephone number is (571) 272-9047. The examiner can normally be reached on 8:00am-5:00pm Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached on (571) 272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/K. R. S./
Examiner, Art Unit 1631

7 October 2008
/John S. Brusca/
Primary Examiner, Art Unit 1631